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EXAMINER

HM42/0922

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ART UNIT	PAPER NUMBER
1616	10

DATE MAILED: 09/22/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 7/13/98 (7/18/97) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 15-34 are pending in the application.
   Of the above, claims 15-29 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 30-34 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This Office Action is a response to the election filed on July 13, 1998. Currently, Claims 15-34 are pending in this application.

In the election response filed on July 13, 1998 a provisional election was made with traverse to prosecute the invention of the composition of claim 31. In terms of applicant's Markush variables, the sub-generic concept wherein the shell material is a protein and the enclosed gas is perfluoropropane, embracing the elected species, is deemed to represent a single inventive concept. Consequently, those species which fall within said sub-generic concept, including those of claim 32-34, are also being examined on their merits. Claim 30 is considered generic to the species set forth above and is only being examined to the extent that it reads upon the elected inventive concept. Affirmation of this election must be made by applicant in responding to this Office action. Claims 15-29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 30-34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time that application was filed, had possession of the claimed invention. In particular, Applicant does not appear to have had possession of the process of forming a composition set forth in the instant claims for the following reasons:

1) Applicant does not appear to have had possession of the specific compositions set forth in dependent claims 31 and 32. Claim 31 is drawn to a composition comprising human protein and perfluoropropane. Claim 32 adds the additional ingredient liposomes. While Applicant's disclosure teaches that human

protein may be used as a shell material[1] and that perfluoropropane may be used as a gas, it fails to teach that the two components would be used in combination with one another. Moreover, the specification fails to specifically set forth that this combination would be used with liposomes. Applicant is thus, in effect, creating new species which were not present in the original specification. *In re Ruschig*[2] states:

> "Disclosure such as that found in formula and words of claim does not amount to a disclosure, sufficient to support a specific claim, of every compound a skilled chemist can see is within scope of that claim; specific claims to single compounds require reasonably specific supporting disclosure; while naming is not essential, something more than disclosure of a class of 1000, 100, or even 48 compounds is required; given time, a chemist could name all of the half million compounds within scope of broadest claim, which claim is supported by broad disclosure; this does not constitute support for each compound individually when separately claimed."

In the instant case, Applicant is creating a new combination of human protein with perfluoropropane, which combination amounts to a sub-genus which was not present in the original specification.

2) The specification fails to teach the combination of two types of microvesicles in one composition, as is apparently intended by the further addition of microspheres in claim 33.

3) The specification fails to teach that a powder would be present in the final composition - which final composition is presumably aqueous if there are microbubbles within it.

Claim[1] rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons:

1) Claim 33 is confusing because it is unclear as to what is meant by microspheres - as distinguished from microbubbles - because the specification sets no clear line of demarcation between the two. There is no indication of what, if any,

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[1] primarily in the context of describing that it has been used as such in the prior art.

[2] 154 USPQ 118, CCPA 1967. see also *Fujikawa v. Wattanasin*, 39 USPQ 2d 1895, CA FC 1996.

would be the shell material and if the gas contained within the microspheres would be the same as the gas within the microbubbles.

2) Claim 34 is confusing because it is unclear as to how one could have a powder and a diluent within a composition that apparently is already in a final aqueous form. In addition the claim is rendered indefinite by the term powder since the specification places no metes and bounds upon the term. Claims must be read in light of the specification but when the specification places no meaning upon a term then that term must be considered indefinite.[3]

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 30-34 are rejected under 35 U.S.C. § 103 as being unpatentable over Rössling et al., (5,501,863; BT; PTO-1449 filed 7/18/97), Tickner (4,265,251; AA; PTO-1449 filed 7/18/97), Schneider et al. (5,531,980; A; PTO-892 dated 7/18/97), Tickner et al. (4,276,885; AB; PTO-1449 filed 7/18/97), Glajch et al. (5,147,631; BG; PTO-1449 filed 7/18/97), Albayrak et al. (WO 90/01952; CL; PTO-1449 filed 7/18/97), Swanson (FG; PTO-1449 filed 7/18/97), in view of Lincoff et al. (FN; PTO-1449 filed 7/18/97), Lincoff et al. (FO; PTO-1449 filed 7/18/97), Jacobs et al. (FQ; PTO-1449 filed 7/18/97), Vygantas et al. (FR; PTO-1449 filed 7/18/97) and the Dupont Technical Bulletin (FT; PTO-1449 filed 7/18/97).

Rössling et al., Reinhardt et al. Tickner '251, Tickner et al. '885, Schneider et al., Glajch et al., Swanson and Albayrak et al. teach that various types of gas filled

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[3] *ex parte Anderson*, 21 USPQ 2d 1241, BdPatApp & Inter, 1992

microspheres may be used for ultrasonic imaging. Each of Rössling et al. Tickner '251, Tickner et al. '885, Glajch et al., Swanson (page 685) and Albayrak et al. further teach genera that include fluorinated gases. In addition, each of Rössling et al. Reinhardt et al. Schneider et al., Tickner '251, Tickner et al. '885, and Albayrak et al. that human protein (including albumin) may be used as the shell material.

Rössling et al. (col. 3, lines 37-41; col. 4, lines 11, 14, 22 & 23) and Reinhardt et al. teach the use of fluorinated gases for ultrasonic imaging and specifically teach two particular fluorinated gases - sulfur hexafluoride and dibromo difluoro methane. Rössling et al. and Reinhardt et al. does not specifically name the particular gases set forth in instant claims 42, 44, and 46; however, Rössling et al. does specifically disclose their hydrocarbon counterparts and then particularly states that they may be halogenated (while disclosing a fluorinated example).

In the case of Schneider et al., Tickner (col. 6; lines 62-68) and Tickner et al., the fluorinated gas taught is Freon®. The term Freon® actually represents a well defined class of small halogen containing molecules, many of which are extremely insoluble in aqueous solution. The Dupont Technical Bulletin teaches that several of the claim designated fluorinated molecules are a well known and explicitly exemplified sub-group of the compounds encompassed by the term Freon®. In particular, the claim designated perfluoropropane[4] is a Freon® (Freon®-218). Consequently, when taken with the Dupont Technical bulletin, the disclosures of Schneider et al, Tickner and Tickner et al. clearly teach fluorinated gases.

Glajch et al. (abstract; col. 6; lines 58-66) teach microparticles containing a gas for ultrasonic imaging and specifically teach perfluoromethane and perfluoroethane. Glajch et al. (col. 7, lines 37-52) also teach that their particles may be mixed with a saccharide dilutant.

Albayrak et al. (pages 3-4[5]; examples 3 and 13) teach perfluorinated gases such as sulfur hexafluoride are particularly suitable for ultrasonic imaging. While Albayrak et al. does not specifically teach that their composition would contain

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[4]perfluoropropane is synonymous with octafluoropropane.

[5]the page numbers cited are actually from the Australian translation. However, it is the WPO document that is being applied as a reference.

microbubbles, Albayrak et al. does teach (pages 4 and 5) that once the composition is mixed with an aqueous solution (as would happen *in vivo*), the insoluble gas would form microbubbles.[6] Albayrak further teaches that albumin may be added to the composition.

Swanson et al. (page 685) teach that a variety of compositions have been used, including microbubbles and highly fluorinated emulsions and further teach that they may be improved by using insoluble gases such as perfluorocarbons.

Lincoff et al., Lincoff et al., Vygantas et al. and Jacobs teach the desirability of using several small perfluorinated molecules[7] *in vivo* because of their stability, safety, and acceptable acoustic properties. Thus, said references provide motivation for particularly selecting said perfluorinated molecules from among the possible gases to be used in each of Rössling et al., Reinhardt et al., Schneider et al., Tickner '251, Tickner et al. '885, Glajch et al., Swanson, and Albayrak et al. particularly teach perfluorocarbons that are gases at 37° C[8].

In addition, the Lincoff publications specifically teach perfluoropropane. Thus, said references provide motivation for particularly selecting this specific fluorinated gas from among the genera of possible gases to be used in each of Rössling et al., Reinhardt et al., Schneider et al. Tickner '251, Tickner et al. '885, Swanson, Glajch et al., and Albayrak et al. Moreover, The Lincoff publications teach the equivalency of perfluoromethane and perfluoroethane with perfluoropropane.

Since each of Rössling et al., Reinhardt et al., Schneider et al. Tickner '251, Tickner et al. '885, Swanson, Glajch et al., and Albayrak et al. teach that their microbubble compositions would be useful for ultrasonic imaging, all of them may be considered to be in the same field of endeavor. While the Lincoff et al. publications and Vygantas et al. are not directed towards ultrasonic imaging and

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[6]please note that the fact that the clathrate composition would form microbubbles once it was mixed with an aqueous solution was not appreciated at the time that the reexamination grant was written and is the reason that Albayrak et al. is now being applied as a reference.

[7]including sulfur hexafluoride, perfluoroethane, perfluoropropane, and perfluorobutane.

[8]Which would include C_1F_4 - C_5F_{12}.

thus could not be considered to be within the same field of endeavor as the references cited above, they specifically address the importance and the usefulness of small perfluorocarbon gases in vivo; giving particular attention to the long persistence of their effect due to their insolubility. Thus, they are pertinent to the problem that inventors in the ultrasonic imaging arts were trying to solve at the time of the invention. Reinhardt et al., Tickner et al. (col. 4, lines 16-29), Swanson (page 684) and Rössling et al. specifically address the importance of finding a gas which has a long duration in the blood and note low solubility as a criteria. In addition, Jacobs serves as a bridge between the ultrasonic imaging arts and the therapeutic art in that Jacobs also is primarily concerned with the therapeutic uses of the perfluorocarbon gases yet also teaches that ultrasonic imaging techniques may be applied to bubbles of perfluorocarbon gases. While the type of large bubble ultrasonic imaging used by Jacobs is not the same as microbubble imaging, it still serves as a bridge in that a person of ordinary skill, while searching through the ultrasonic imaging literature, would find a cross reference to Jacobs and thus find further information about the duration problem they were attempting to solve. It is also important to note that Lincoff et al., Lincoff et al., Vygantas et al. and Jacobs teach that small fluorinated molecules are safe in quantities that are orders of magnitude beyond the quantities injected in a bolus of microbubbles. This is also a problem that would be extremely pertinent when determining what gas to use in an *in vivo* ultrasonic imaging procedure.

While none of Rössling et al., Reinhardt et al., Schneider et al., Tickner '251, Tickner et al. '885, Swanson, Glajch et al., and Albayrak et al. specifically teach perfluoropropane, it would have been obvious to those of ordinary skill in the art that perfluoropropane could be used because said references each teach genera which clearly encompass perfluoropropane. One of ordinary skill would have been motivated to particularly select perfluoropropane because Lincoff et al., Lincoff et al., Vygantas et al. and Jacobs teach that low molecular weight perfluorocarbons (including specifically perfluoropropane) solve the particular problem of other gases short duration and further teach that said gases are safe in much larger quantities

than would be required for ultrasonic imaging. In addition, Glajch et al. specifically teach that one[9] of the claim designated gases is useful for ultrasonic imaging.

The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Claims 30-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. patent nos. 5,409,688, 5,393,524, 5,573,751, 5,558,854, 5,558,094, 5,558,855, and 5,558,853 because the instant elected composition is drawn to a specific sub-genus which would be encompassed within the broader claims of the cited patents.

Claims 30-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending application serial no. 08/466,104, 08/646,910, 08/710,849, 08/770,522, 08/745,256, and 08/900,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant elected composition is drawn to a specific sub-genus which would be encompassed within the broader claims of the cited applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

> The obviousness-type double patenting rejection, whether of the obviousness type or non-obviousness type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent[10].
>
> A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

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[9]the gas specifically taught is perfluoroethane.

[10]*In re Thorington*, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 214 USPQ 761 (CCPA 1982); *In re Longi*, 225 USPQ 645 (CA FC 1985); and *In re Goodman*, 29 USPQ 2010 (CA FC 1993).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 30 and 31 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of the claims of copending application Serial No. 08/710,849. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. § 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ...". Thus, the term "same invention," in this context means an invention drawn to identical subject matter[11].

A statutory type (35 U.S.C. § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are not longer coextensive in scope. The filing of terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. § 101.

In view of the objections /rejections to the pending claims set forth above, no claims may be allowed at this time.

Examiner Hollinden has moved to Art Unit 1616. Please include the new Art Unit number on all future correspondence as it will greatly expedite handling of papers.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to the Group 1600 fax machine at 703/308-4556. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30; November 15 1989.

Any inquiry concerning this Office Action or any earlier Office Actions in this application should be directed to Dr. Gary E. Hollinden whose telephone number is

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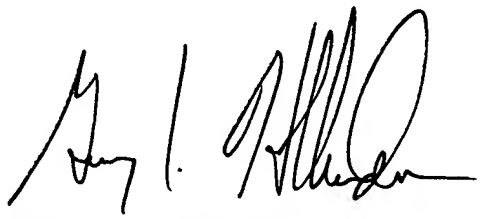
[11] *Miller v. Eagle Mfg.* 151 U.S. 186 (1894); *In re Ockert*, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 164 USPQ 619 (CCPA 1970).

703/308-4521. Dr. Hollinden's office hours are from 6:30 am to 3:00 pm, Monday through Friday.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is 703/308-1235.



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